In the Office Action, the Examiner rejected claims 1-4 and 9-32 under 35 USC §103(a) as being unpatentable over DeLuca et al U.S. Patent 5,945,410. The Examiner states that the DeLuca et al '410 patent teaches a generic group of 2-alkyl-19-nor-vitamin D compounds and exemplifies in particular 19-nor-2-methyl-1α,25-dihydroxyvitamin D_3. Accordingly, the compounds taught in the '410 reference are adjacent lower homologs of the claimed compounds which are isomeric forms of 19-nor-2-ethyl-1α,25-dihydroxyvitamin D_3. Thus, the Examiner concludes that the close structural similarity of the prior art compounds makes the instantly claimed compound obvious. In addition, the Examiner notes that the data presented in Table 1 of the present specification is not a comparison with the closest prior art compounds, and thus the examiner does not consider the results presented to adequately support unobviousness and/or any unexpected properties of the instantly claimed compounds.

The Examiner correctly notes that the '410 patent teaches that the 2-alkyl-19-nor-vitamin D compounds are characterized by low intestinal calcium transport activity and high bone calcium mobilization activity. For example, it is stated at column 3, line 67 through column 4, line 5 that

> "These compounds are characterized by little, if any intestinal calcium transport activity, as compared to that of 1α,25-dihydroxyvitamin D_3, while exhibiting relatively high activity, as compared to 1α,25-dihydroxyvitamin D_3, in their ability to mobilize calcium from bone."

More specifically, Applicant refers the Examiner to column 15, line 30 through column 16, line 21 and the data in Table 1 of the '410 patent where the biological activity of the α and β isomers of the 2-methyl-19-nor-1α,25-dihydroxyvitamin D_3 compounds and their 20S-isomers is disclosed and discussed. These are the compounds specifically referred to by the Examiner as the closest prior art compounds to Applicant's instantly claimed 2-ethyl compounds. More particularly, with respect

to the 2-methyl-20S compounds, and the 2-methyl compounds in the '410 patent, it is stated at column 15, lines 60 through column 16, line 7 that

> ". . . the most potent compounds tested where a mixture of the S and R isomers of 2-methyl-19-nor-20S-1,25-$(OH)_2D_3$ (Table 1). When given at 130 pmol/day, the activity of this mixture of compounds on bone calcium mobilization (serum calcium) was much higher than that of the native hormone, possibly as high as 10 or 100 times higher.
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> To show its selectivity, these compounds produced no significant change in intestinal calcium transport at 130 pmol dose level while having a strong bone calcium mobilizing activity.
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> * * *
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> A mixture of the S and R isomers of 2-methyl-19-nor-1,25-$(OH)_2D_3$ also had strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. Thus, the 2-methyl-S and R derivatives given as a mixture showed strong preferential bone calcium mobilizing activity especially when the side chain was in the 20S configuration. These results illustrate that the 2-methyl and the 20S-2-methyl derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from bone. Table 2 illustrates the responses of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1."

As the Examiner can see, the 2-methyl and 2-methyl-20S compounds disclosed in the '410 reference are characterized by low intestinal calcium transport activity and high bone calcium mobilization activity as compared to 1α,25-dihydroxyvitamin D_3.

In contrast, however, the instantly claimed 2-ethyl compounds have different biological activities. As stated at page 22, line 28 through page 23, line 2 and the data in Table 1 at pages 23 and 24 of the present specification, the 2-ethyl-19-nor vitamin D compounds

> ". . . have some ability to mobilize calcium from bone but not to the extent of the hormone 1, while being inactive in intestine. The only exception is 2α-ethyl isomer from 20S-series that shows strong calcium mobilization response and marked intestinal activity."

A review of the data in Table 1 (at page 24 of the specification) clearly shows that the 2α-ethyl-19-nor compound 6a as well as the 2β-ethyl-19-nor compound 7a and 2β-ethyl-19-nor compound 7b have little, if any, intestinal calcium transport activity. This calcium transport activity is similar to that set forth with respect to the 2-methyl lower homologs taught in the '410 patent. However, these same compounds (6a, 7a and 7b) all have "some ability to mobilize calcium from bone but not to the extent of hormone 1". This can be seen from the data in Table 1 wherein compounds 6a, 7a and 7b all have serum calcium readings of 5.1 +/- 0.1, 5.0 +/- 0.1 and 5.6 +/- 0.1 as compared to 5.8 +/- 0.1 for 1α,25-dihydroxyvitamin D_3 and 3.9 +/- 0.1 for control. Thus, these three compounds have bone calcium mobilization activity which is much higher than control, but only slightly less than 1α,25-dihydroxyvitamin D_3. In contrast, the 2-methyl homologs taught in the '410 patent have bone calcium mobilization activity that is higher than 1α,25-dihydroxyvitamin D_3. Thus, even though these three compounds are structurally similar to the prior art compounds disclosed in the '410 patent, and as a result would be expected to have similar biological activities, it is clear from the data in Table 1 that their activities are not similar but instead are different and distinct.

With respect to the 2α-ethyl-19-nor compound 6b, the data in Table 1 show that this compound has some intestinal calcium transport activity. Although this activity is less than the activity reported for 1α,25-dihydroxyvitamin D_3 (i.e. 5.0 +/- 0.4 versus 6.5 +/- 0.9) it can be said that it clearly does have intestinal calcium transport activity since the value reported is much higher than the control value of 3.8 +/- 0.4. With respect to bone calcium mobilization activity, the 2α-ethyl-19-nor compound 6b has higher activity than 1α,25-dihydroxyvitamin D_3 as evidenced by the values of 7.0 +/- 0.1 versus 5.8 +/- 0.1. In contrast, however, the 2-methyl homologs disclosed in the '410

patent have little, if any, calcium transport activity and have higher bone calcium mobilization activity when compared to 1α,25-dihydroxyvitamin D_3. Thus, once again, the 2α-ethyl-19-nor compound 6b disclosed and claimed herein is distinguishable both structurally and via its biological activity from the closest prior art compounds. Again, due to their structural similarity, it would be expected that this compound have the same or similar biological activities as the 2-methyl prior art compounds disclosed in the '410 patent. However, it is clear from the above comparison that it is both structurally and functionally different from the closest prior art compound.

As a result, Applicant believes that the rejection of claims 1-4 and 9-32 as being unpatentable over the '410 patent should be withdrawn.

In the Office Action, claims 5-8 and 33-56 were rejected under 35 USC §103(a) as being unpatentable over DeLuca et al U.S. Patent 5,843,928. The Examiner states that DeLuca et al '928 teaches a generic group of 2-akylidene-19-nor-vitamin D compounds and exemplifies isomeric forms of 19-nor-2-methylene-1α,25-dihdroxyvitamin D_3. Since the compounds disclosed in the '928 reference are adjacent lower homologs of the instantly claimed compounds, the close structurality renders the instantly claimed compounds obvious.

The Examiner correctly notes that the '928 patent states that the compounds disclosed therein are characterized by low intestinal calcium transport activity and high bone calcium mobilization activity. At column 4, lines 7-12 it is stated

> "These compounds are characterized by little, if any, intestinal calcium transport activity, as compared to that of 1α,25-dihydroxyvitamin D_3 while exhibiting relatively high activity, as compared to 1α,25-dihydroxyvitamin D_3 in their ability to mobilize calcium from bone."

In addition, Applicant refers the Examiner specifically to column 15, line 34 through column 16, line 22 of the '928 patent where the biological activity of the 2-methylene

compounds and their 20S isomers are disclosed and discussed. More specifically, it is stated at column 15, line 63 through column 16, line 19 that

> "When given for 7 days in a chronic mode, the most potent compound tested was the 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ (Table 1). When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the order of at least 10 and possible 100-1,000 times more than that of the native hormone. Under identical conditions, twice the dose of 1,25-$(OH)_2D_3$ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone.
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> * * *
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> To show its selectively, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-$(OH)_2D_3$ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day. The 20-methylene-19-nor-1,25-$(OH)_2D_3$ also had extremely strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. The bone calcium mobilization activity of this compound is likely to be 10-100 times that of 1,25-$(OH)_2D_3$. These results illustrate that the 2-methylene and the 20S-2-methylene derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from bone. Table 2 illustrates the response of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1."

Thus, it is clear that the 2-methylene prior art compounds, i.e. the closest prior art compounds, show little, if any, intestinal calcium transport activity while exhibiting bone calcium mobilization activity that is significantly higher than 1α,25-dihydroxyvitamin D_3.

In contrast, and turning to Applicant's claimed compounds, Applicant refers the Examiner to the discussion at page 22, lines 26-28 and the data in Table 1 on page 23 of the specification as filed. As illustrated and discussed therein, both E-isomers of the 2-

ethylidene-19-nor-vitamins, i.e. compounds 4a and 4b exhibit very high calcemic activity which is higher than 1α,25-dihydroxyvitamin D_3 compound 1. At 130 pmols, compound 4a has calcium transport activity of 6.8 +/- 0.4 and compound 4b has a calcium transport value of 5.8 +/- 0.8 as compared to compound 1 value of 5.5 +/- 0.5. With respect to bone calcium mobilization activity, both E-isomers have serum calcium activity that can be characterized as the same or higher than 1α,25-dihydroxyvitamin D_3. In summary, these compounds have intestinal calcium transport activity which is higher than 1α,25-dihydroxyvitamin D_3 and bone calcium mobilization activity that is the same or higher than 1α,25-dihydroxyvitamin D_3. In contrast, the 2-methylene compounds of the '928 patent have little, if any, intestinal calcium transport activity and higher bone calcium mobilization activity than 1α,25-dihydroxyvitamin D_3. Thus, the instantly claimed E-isomers are not only structurally different, but they have different biological activities. Although structurally they are homologs of the '928 prior art compounds, and would thus be expected to have the same or similar biological activities, it is clear from the above comparison that the two E-isomers have different biological activities than the closest prior art compounds.

With respect to the two Z-isomers claimed by Applicant, the data in Table 1 once again show that these two compounds are different from the closest prior art compounds. With respect to intestinal calcium transport activity, compound 5a has activity which is about the same as 1α,25-dihydroxyvitamin D_3 as illustrated by the values of 5.7 +/- 0.9 versus 5.5 +/- 0.5 at 130 pmols. With respect to bone calcium mobilization activity, compound 5a has little, if any, activity as illustrated by the value 4.2 +/- 0.0 versus 4.3 +/- 0.1 for control. Thus, compound 5a is distinguishable from the closest prior art compounds since it has substantially the same intestinal calcium transport activity as 1α,25-dihydroxyvitamin D_3 and has little, if any, bone calcium mobilization activity as compared to 1α,25-dihydroxyvitamin D_3. The Examiner will remember that the 2-methylene closest prior art compounds had little, if any, intestinal calcium transport activity and relatively high bone calcium mobilization activity when

compared to 1α,25-dihydroxyvitamin D_3. Thus, compound 5a is both structurally and functionally different from the closest prior art compounds.

With respect to the Z-isomer compound 5b, this compound is also distinguishable from the prior art. The data in Table 1 at page 23, show that compound 5b has little, if any, intestinal calcium transport activity and little, if any, bone calcium mobilization activity since the values of 3.8 +/- 0.3 and 4.0 +/- 0.1 are substantially the same as control. In contrast, although the 2-methylene prior art compounds of the '928 patent had little, if any, intestinal calcium transport activity, they had higher bone calcium mobilization activity than 1α,25-dihydroxyvitamin D_3. Again, compound 5b is both structurally and functionally different from the closest prior art compounds. Although it is a homolog of these prior art compounds, and would thus be expected to have similar activities, it is clear from the above comparison that its biological activities are different from the prior art compounds.

As a result, Applicant believes the Examiner should withdraw the rejection of claims 5-8 and 33-56 under 35 USC §103(a).

In the Office Action, the Examiner rejected claims 1-4 and 9-32 under the Doctrine of Obviousness Type Double Patenting as being unpatentable over claims 1, 2, 7 and 12-20 of U.S. Patent No. 5,945,410. The Examiner indicated that since the present application claimed a homolog of the compound exemplified in the '410 patent, it would be expected that the homologs would have the same properties and thus have similar uses as taught by the '410 reference.

However, as discussed previously herein, the compounds of claims 1-4 and 9-32 do not have the same properties as the compounds claimed in the '410 patent. Thus, as stated by the Examiner, since the compounds of claims 1-4 are homologs of the compounds disclosed in the '410 patent, one would expect their activities to be substantially the same. As noted above, these activities are not substantially the same resulting in the compounds of claims 1-4 not being obvious in view of the compounds

disclosed in the '410 patent. Thus, Applicant requests the Examiner withdraw the obviousness type double patenting rejection of claims 1-4 and 9-32.

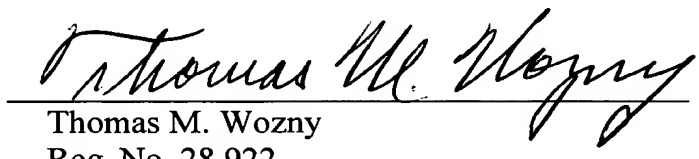
In the Office Action, the Examiner rejected claims 5-8 and 33-56 under the Doctrine of Obviousness Type Double Patenting as being unpatentable over claims 1, 2, 7 and 12-16 of U.S. Patent No. 5,843,928. The Examiner indicated that since the present application claimed a homolog of the compound exemplified in the '928 patent, it would be expected that the homologs would have the same properties and thus similar use as taught by the '928 reference.

However, as discussed previously herein, the compounds of claims 5-8 and 33-56 do not have the same properties as the compounds claimed in the '928 patent. Thus, as stated by the Examiner, since the compounds of claims 5-8 are homologs of the compounds disclosed in the '928 patent, one would expect their activities to be substantially the same. As noted above, these activities are not substantially the same resulting in the compounds of claims 5-8 not being obvious in view of the compounds disclosed in the '928 patent. Thus, Applicant requests the Examiner withdraw the obviousness type double patenting rejection of claims 5-8 and 33-56.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

ANDRUS, SCEALES, STARKE & SAWALL, LLP

By 

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